Original Article

A Study of the Etiology and Bleeding Manifestations in Patients of Acute Fever with Thrombocytopenia

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Abstract

Background : In a tropical country like India, people with acute febrile illness are more likely to have an infectious aetiology and may have associated thrombocytopenia.

Materials and Methods : Over a period of 18 months, 80 patients from 18 to 90 years of age, male and female, with history of fever of acute duration with thrombocytopenia (platelet count less than 1,50,000/mm^3 on admission) admitted in BHRC, Pune were selected by using simple random method. The study was conducted after ethical clearance from the Ethics Committee.

Results : 57(71.25%) were males and maximum patients were in the age group 21 to 30 years (31.2%). Maximum number of patients presented with 1-3 days of history of fever (n=48, 60%). The maximum number of cases suffered from dengue (n=46 57.5%), followed by Malaria (n=16, 20 %) and COVID-19 (n=9, 11.3%). In cases reporting to hospital after more than 5 days of fever (n=4, 5%) had a higher median of platelet count, 78,000/mm^3. The most common physical manifestation of thrombocytopenia was petechiae (8.8%). In 50% of septicaemia cases displayed petechiae. Malaria cases displayed petechiae (18.75%).

Conclusion : As the duration of fever progressed from day 1 to day 6 the Platelet count also showed decreasing trends. Petechiae were the most common manifestation, followed by hematuria, per rectal bleed and epistaxis. The major causes of bleeding manifestations of patients in our study were septicemia and leptospira, followed by Malaria, Dengue and COVID-19.

Key words : Fever, Dengue, Platelets.

Febrile is derived from the word 'febris' which means fever in Latin. Pyrexia is another word for fever, derived from the Greek word 'pyretus' meaning fire.

Fever is considered one of the body's immune mechanisms to neutralize the perceived threat inside the body[1]. Febrile thrombocytopenia, defined as a platelet count less than 1,50,000/mm^3 along with an increase in average body temperature of 98.6 degrees Fahrenheit (37 degrees Celsius), can be associated with many viral, bacterial, autoimmune and idiopathic conditions. The normal platelet count is 1,50,000-4,50,000/mm^3. Platelets are generally derived from the bone marrow from their progenitor cells known as megakaryocytes and have a life span of 10 days. Thrombocytopenia is seen due to diminished production, augmented sequestration or destruction of platelets[1]. There has been a rise in the number of patients with fever and thrombocytopenia recently. Common causes of fever with thrombocytopenia include Dengue, Malaria, Leptospirosis, Chikungunya, Kyasanur Forest Diseases, Scrub Typhus, Miliary Tuberculosis, Typhoid, Human Immunodeficiency Virus (HIV) and recently, Coronavirus Disease-19 (COVID-19). This study demonstrates the correlation between platelet counts and bleeding manifestations to enable us to estimate the correct timing for transfusion of platelets to avoid needless platelet transfusions to such patients.

Editor's Comment :

- It is imperative that we analyze low platelet count as one of the diagnostic marker of common infections and form a systematic approach that is conducted with an awareness of different causes of fever with thrombocytopenia, streamlining the differential diagnosis and specific etiology.
- This study demonstrates the correlation between platelet counts and bleeding manifestations to enable us to estimate the correct timing for transfusion of platelets to avoid needless platelet transfusions to such patients.

Materials and Methods

The study was conducted after ethical clearance from the Ethics Committee at Bharati Vidyapeeth Deemed University Medical College and Hospital, Pune.

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Biochemical and pathological analysis was done in the Department of Biochemistry and Department of Pathology, Bharati Hospital and Research Centre (BHRC), Pune. With adherence to the Helsinki declaration, informed consent in the prescribed format was obtained from all patients included in the study after explanation of the probable benefits in local language. Over a period of 18 months, 80 patients from 18 to 90 years of age, male and female, with history of fever of acute duration with thrombo-cytopenia (platelet count less than 1,50,000/mm^3 on admission) admitted in BHRC, Pune were selected by using simple random method. Exclusion criteria included: patients with febrile thrombocytopenia due to non-infective etiology like immune thrombo-cytopenia, drug-induced thrombocytopenia, hemolysis, elevated liver enzymes and low platelets (HELLP syndrome), myelo-proliferative diseases, disseminated intravascular coagulation of non-infective etiology (abruptio placentae, snake bite), patients with chronic liver disease, and patients with autoimmune disease. One standard questionnaire was used for each patient including personal data, demographic information, detailed history of present illness, drug usage, past disease history and physical examination. Risk factors such as Hypertension, Diabetes Mellitus, coagulopathy and autoimmune diseases were noted. Relevant laboratory investigations were sent including Complete Blood Count (including Total Leucocyte Count, Platelet Count), Renal Function Test, Liver Function Test, PT and INR, and urine routine. Tropical fever workup and other special investigations (including ECG, USG abdomen pelvis, X-ray chest) were done if clinically indicated. Platelet count estimation was done using electrical impedance method in the automated hematology analyzer in the BHRC laboratory. Repeat platelet count was done on day 3, day 5 and then on discharge in patients with platelet count between 40,000/mm^3 - 1,50,000/mm^3.

Random/single donor Platelet transfusion was considered in patients with Platelet count of 10,000/mm^3 as absolute indication with or without bleeding manifestations. Relative indications included Platelet countless than 20,000/mm^3 and presence of bleeding manifestations regardless of platelet count.

Results

The study subjects were in the range of 18 to 78 years. Out of 80 patients, 57 (71.25%) were males and 23 (28.75%) were female. Maximum patients were in the age group 21 to 30 years (31.2%).

Maximum number of patients presented with 1-3 days of history of fever (n=48, 60%), followed by history of fever since 4-5 days (n=28, 35%) and history of fever since more than 5 days (n=4, 5%).

The minimum Platelet count was 10,000/mm^3. Maximum was 1,49,000/mm^3. The cases who reported within 1 to 3 days of the start of fever (n=48, 60%) were more likely to present with a higher platelet count (median = 49,500/$mm^{3)}$. The cases who reported to hospital within 4 to 5 days of onset of fever (n=28, 35%) had a lower overall platelet count with a median of 47,500/mm^3. In cases reporting to hospital after more than 5 days of fever (n=4, 5%) had a higher median of platelet count, 78,000/mm^3; however, the frequency of cases below the median was higher.

The maximum number of cases suffered from Dengue (n=46 57.5%), followed by Malaria (n=16, 20%) and COVID-19 (n=9, 11.3%). Swine flu and viral fever had the minimum number of cases (n=1, 1.3 % each).

Patients suffering from septicaemia had the highest incidence headache with 100% patients complaining of headache. Further, patients suffering from COVID-19 had maximum incidence of symptoms of arthralgia/myalgia- 66.67% and headache- 88.89%, while dengue patients suffered from the same at 45.65% and 65.22%, respectively.

Nausea and vomiting seen most frequently in viral fever, enteric fever and leptospirosis (100% in all), followed by Dengue 67.39% and Malaria 62.5%.

Altered sensorium was seen in 22.22% of COVID-19 patients.

Out of the subjects studied, majority of the patients did not have any active bleeding manifestations (76.3%) despite having thrombocytopenia. The most common physical manifestation of thrombocytopenia was petechiae (8.8%). 50% of Septicaemia cases displayed petechiae. Malaria cases displayed petechiae (18.75%), followed by menorrhagia and bleeding per rectum (PR) (6.25% each). Dengue cases showed a wide variety of bleeding manifestations with 6.52% demonstrating petechiae followed by epistaxis (4.35%) and hematuria (4.35%). In 11.11% of COVID-19 positive patients showed ecchymotic patches. None of the cases with enteric fever, swine flu or viral fever showed any bleeding manifestations.

Discussion

In our study, a majority of patients belonged to the

age group of 21-30 years, followed by 31-40 years. A similar study by Gondhali et al also reported the maximum cases in the age group of 21-30 years[2]. In the present study, the male to female ratio was 2.5:1. As in our study, several other studies on febrile thrombocytopenia have reported male preponderance, including Choudhary, *et al*, Radhika, *et al*, Sumangala et al and Naikwadi, *et al*[3-6].

Maximum number of patients presented with 3 days of history of fever (31.25%), followed by history of fever since 2 days (22.5%), followed by 20% of patients who had history of fever since 4 days.

A study by Fah, *et al* reported that patients presented with fever ranging from 2-10 days[7]. Kandagatla, *et al* reported that all patients showed unspecified fever, with the duration varying from 1-5 days to >15 days, while most of them exhibited fever in first 5 days (65%)[8].

In our study, the median platelet count on day 1 of admission was 49,000/mm^3, with the minimum being 10,000/mm^3 and maximum being 1,49,000/mm^3. Nair et al displayed a platelet count range of >50,000/mm^3 in 83 (46.11%) patients, 20000-50000/mm^3 in 43 (23.89%) and <20,000/mm^3 in 54 (30%) of patients. Radhika, *et al* displayed platelet count <20,000/mm^3 in 35 (4%) cases. Naikwadi, *et al* demonstrated <50,000/mm^3 in 18 (18%) patients[4,6,9].

In our study, classifying the Platelet count further based on the duration of fever at the time of hospital admission, 60% of patients who had duration of fever of 1-3 days at the time of admission to hospital had a median platelet count of 49,500/mm^3. Jayanthi, *et al* studied the correlation between Platelet count and other parameters to the duration of hospital stay in dengue fever with thrombocytopenia. They found that there was a significant negative correlation between platelet count and duration of hospital stay, which could be explained as number of complications increasing as the platelet count decreased[10].

The first three causes of febrile thrombocytopenia in our study are Dengue (57.50%), Malaria (20%) and COVID-19 (11.25%), followed by Enteric fever (3.75%), Leptospira and Septicemia (2.5% each) and Swine flu and Viral fever (1.25%). Lohitashwa, *et al* had similar findings for Dengue and Nair, *et al* showed similar numbers for Septicemia[11,9]. Bhalara, *et al* found the causes of febrile thrombocytopenia in their study to be Dengue (28.6%), Malaria (22.8%) and septicaemia (6.3%)[12]. Sumangala, *et al* found the causes to be Dengue (53%), Malaria (15.6%) and septicaemia (8.7%)[5].

As Dengue fever was the major etiological disease in our case study, we studied it in detail. The median Platelet count was found to be 45,000/mm^3, with 50% patients having a Platelet count between 25,000 and 86,000/mm^3. Nelson, *et al* reported that 85% patients with Dengue had a thrombocytopenia with a Platelet count below 1,05,000/mm^3.[13]

Malaria was the second most common etiology for thrombocytopenia in our study (20%). Malaria patients usually developed thrombocytopenia around 3-5 days of fever. according to presence of thrombocytopenia was not a distinguishing feature between the two types of malaria Jadhav, *et al*[14].

In a study on over two thousand patients with fever, Erhart, *et al* reported platelet count of less than 1,50,000/mm^3 increases the likelihood of Malaria by 12-15 times. Various other studies have also found thrombocytopenia to be commonly associated with malaria, which resolves after therapy[15].

In both COVID-19 and Dengue infection, patients can present with overlapping clinical features such as fever and myalgia as well as thrombocytopenia.

In our study, of all the patients presenting to the hospital with 3, 4 or 5 days of fever, the most common aetiology was dengue, followed by malaria and COVID-19.

In our study, arthralgia and myalgia were found in 42.5% of cases. Fah, *et al* reported arthralgia/myalgia and nausea/ vomiting in 69.7% cases in their study[7].

In our study, headache was also reported by 66.25% cases of all aetiologies except swine flu and viral fever. Gajbhare, *et al* reported headache in 44% of cases in their study, while Kandagatla, *et al* reported headache in 30.63% cases[16,8].

In our study, altered sensorium was reported by 5% of cases. In a study by Gondhali, *et al* altered sensorium was reported in 15% of cases[3].

In our study, 25% cases presented with bleeding manifestations. Petechiae (8.75%) was the major presentation, followed by hematuria (3.75%) and epistaxis, menorrhagia and PR bleed (2.5 % each) in our study. Lohitashwa, *et al* had bleeding manifestations in 49% of patients with 63% showing petechiae. Nair, *et al* had 41% bleeding with 22.22% petechiae.

In our study, 44% patients with severe thrombocytopenia (platelet count between 20,000- 50,000/mm^3) experienced bleeding manifestations, while only 3.7% patients with moderate thrombocytopenia had bleeding manifestation .

Similar to our study, several studies including Harsha, *et al*; Kashiv, *et al* and Gondhali, *et al* have reported that bleeding manifestations were more frequent when the platelet counts were <20,000/mm^3.[17,18, 2]

In our study, ecchymosis was the only bleeding manifestation observed in COVID-19 patients (11.1%). A maximum variety of bleeding manifestation was observed in dengue patients, with 6.52% reporting petechiae, 4.35% reporting epistaxis and hematuria, followed by 2.17% of patients reporting hematemesis, malena, menorrhagia and per rectal bleed. In malaria patients, petechiae were reported by 18.75% patients followed by menorrhagia and per rectal bleed which was reported by 6.25% patients each, in our study.

In comparison, in a study by Nelson et al on dengue patients, 72% had hemorrhagic skin manifestations, most often a subtle petechiae eruption on the extremities. Epistaxis was found in 17%; gastro-intestinal hemorrhage 11%, 45% had menstrual irregularities, 17% had no hemorrhagic findings[13].

Gondhali, *et al* reported that 6 (10.71%) out of 56 patients had bleeding[2].

Study Limitations : The COVID-19 pandemic broke out after this study was initiated. Hence recruitment of subjects in the study was delayed and was not a true representation of cases of the pre- COVID-19 era. Our study sample was small and also included only a single centre and hence the adequate representation of the entire population cannot be made.

Conclusion

Maximum patients of fever with thrombocytopenia were in the age group of 21-30 years. The male: female ratio was 2.5:1. Duration of fever at the time of admission had significant correlation with thrombocytopenia. As the duration of fever progressed the platelet count also showed decreasing trends. The most common etiology of thrombocytopenia in our study was Dengue, followed by Malaria and COVID-19. Petechiae were the most common manifestation, followed by hematuria, per rectal bleed and epistaxis.The major causes of bleeding manifestations of patients in our study were Septicemia and Leptospira, followed by Malaria, Dengue and COVID-19.

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Conflict of Interest : None

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